Synthesis of Regio- and Stereospecifically Deuterium Labelled 2-Benzylindanes

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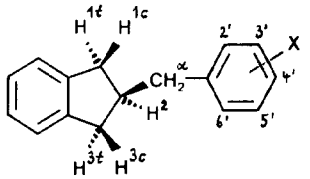
Indanes, Indenes, Deuterium Labelling, Homogeneous Catalytic Hydrogenation, Stereochemistry

2-Benzylindenes (**1, 1a**) are hydrogenated to 2-benzylindanes (**2**) using tris-(triphenylphosphine)-rhodium(I)-chloride in benzene by a strict *cis*-1,2 addition of hydrogen to the double bond. Thus, stereo- and regio-specific deuterium labelling at the five-membered ring of various 2-benzylindanes has been carried out. The high selectivity of deuterium incorporation is shown independently by ^{1}H NMR and mass (MIKE*) spectrometry of selected 2-benzylindanes.

Introduction

In the course of our mass spectrometric investigation of the intramolecular hydrogen exchange in gaseous radical cations of α,ω-diphenylalkanes [1–3] we required a synthetic access to various stereospecifically deuterium labelled 2-benzylindanes **2.**

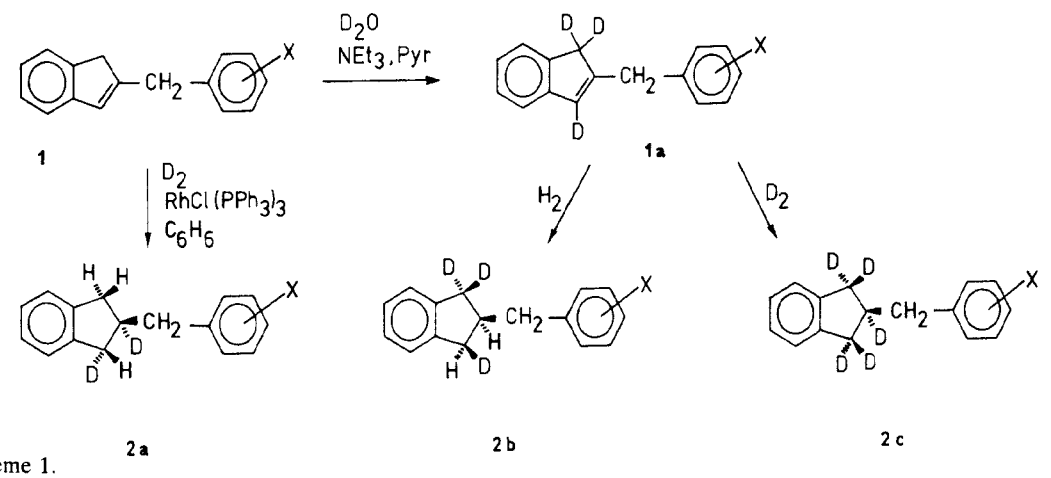


2: X = H, 3′-, 4′-OCH_3, -F, -CH_3, -OH, -$N(CH_3)_2$; 3′,5′-$(OCH_3)_2$

It is well known that in heterogeneous catalytic hydrogenation of alkenes partial isomerization and/or migration of the double bond occurs [5, 6]. In the case of olefins labelled with deuterium at the $\rangle$CH–CH=CH-grouping or of using deuterium gas, non-regio-specific and isotopically impure labelling results [6]. As another consequence, the overall hydrogenation of the alkene may generate, in part, the products of *trans*-addition of H_2 (D_2) to the double bond along with that of *cis*-addition.

Indenes represent a class of alkenes containing a particularly reactive allylic group. Accordingly, heterogeneous catalytic hydrogenation of 2-benzylindenes over various Pt and Pd catalysts in alcoholic solvents, produces 2-benzylindanes with ⩾ 35% incorrect incorporation of the label [7].

We wish to report here on the successful application of tris-(triphenylphosphine)-rhodium(I)-chloride (Wilkinson's catalyst) [8] to the stereo- and regiospecific deuterium labelling of indanes **2** by homogeneous catalytic hydrogenation and deuteration of the corresponding indene precursors **1.**



Scheme 1.

* MIKE spectrometry: Mass analyzed ion kinetic energy spectrometry.

03400–5087/84/0300–0369/$ 01.00/0

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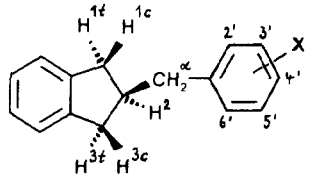

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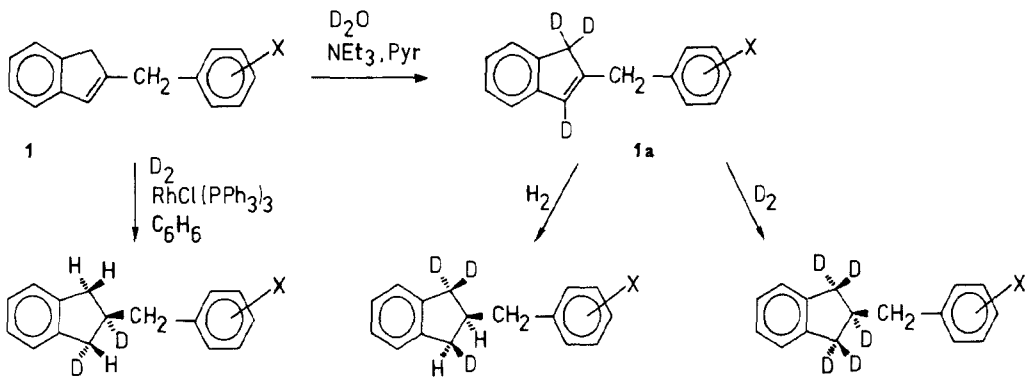

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Results and Discussion

Using $RhCl[P(C_6H_5)_3]_3$ in *ca.* 0.2 m benzene solution hydrogenation of **1** takes place slowly (24–36 h) at room temperature with ≥ 99% regio- and stereoselectivity, as shown by ^1H NMR and mass spectrometry *(vide infra)*. Thus, using D_2 gas, [1*t*,2-D_2]-indanes (**2a**) are obtained from **1** with ≥ 98% isotopic purity. In the same way, [1*c*,3,3-D_3]-indanes (**2b**) and [1,1,2,3,3-D_5]-indanes (**2c**) are produced from 2-benzyl-[1,1,3-D_3]-indenes (**1a**), which are synthesized from **1** by basic H/D exchange [8]. The 2-benzylindanes are isolated in nearly quantitative yields, irrespective of the substituent X (Scheme 1).

The stereo- and regiospecifity of the labelling is shown by ^1H NMR spectrometry of, *e.g.*, the unsubstituted 2-benzyl-[1*t*-2-D_2]-indane (**2a**) (X = H) (Fig. 1) and by mass spectrometry of 2-(3′-methoxybenzyl)-[1*c*,3,3-D_3]-indane (**2b**) (X = 3′-OCH_3) (Fig. 2), respectively. These examples afford complementary structural information and are representative for all of the various substituted and labelled indanes **2.**

2a shows an AB-system ($\delta_H A$ = 2.65 ppm, $\delta_H B$ = 2.95 ppm, $^2J_{AB}$ = −15.8 Hz) due to the C^3 methylene group, a singlet at 2.75 ppm due to the benzylic methylene group, and a broad singlet at δ 2.64 ppm, which has to be assigned to the CHD group ($^2J_{HD}$ is estimated to be *ca.* 2.0 Hz, corresponding to the expected value of *ca.* 0.15 · $^2J_{HH}$ [9]). Since the shielding of a proton at five-membered rings by a vicinal *cis*-substituent is well known [10], we have to assume that $H^A = H^{3c}$ and $H^B = H^{3t}$. Hence, the resonance at δ 2.64 ppm reflects the *cis*-position of the CHD-proton (H^{1c}), showing an isotope effect ($\Delta\delta$ = −17 ppm) of reasonable magnitude [11]. There is no resonance within the region of the H^B signals (see sinuous arrow in Fig. 1); hence, the *trans*-C^1 position bears no hydrogen but rather ≥ 99% deuterium atoms (D^{1t}). In turn, it follows that no deuterium is incorporated in the C^3 methylene group.

This interpretation of the ^1H NMR spectrum, showing stereo- and regiospecific deuteration of **1,** is corroborated by the mass spectrometric analysis of the complementarily labelled indane **2b** (X =

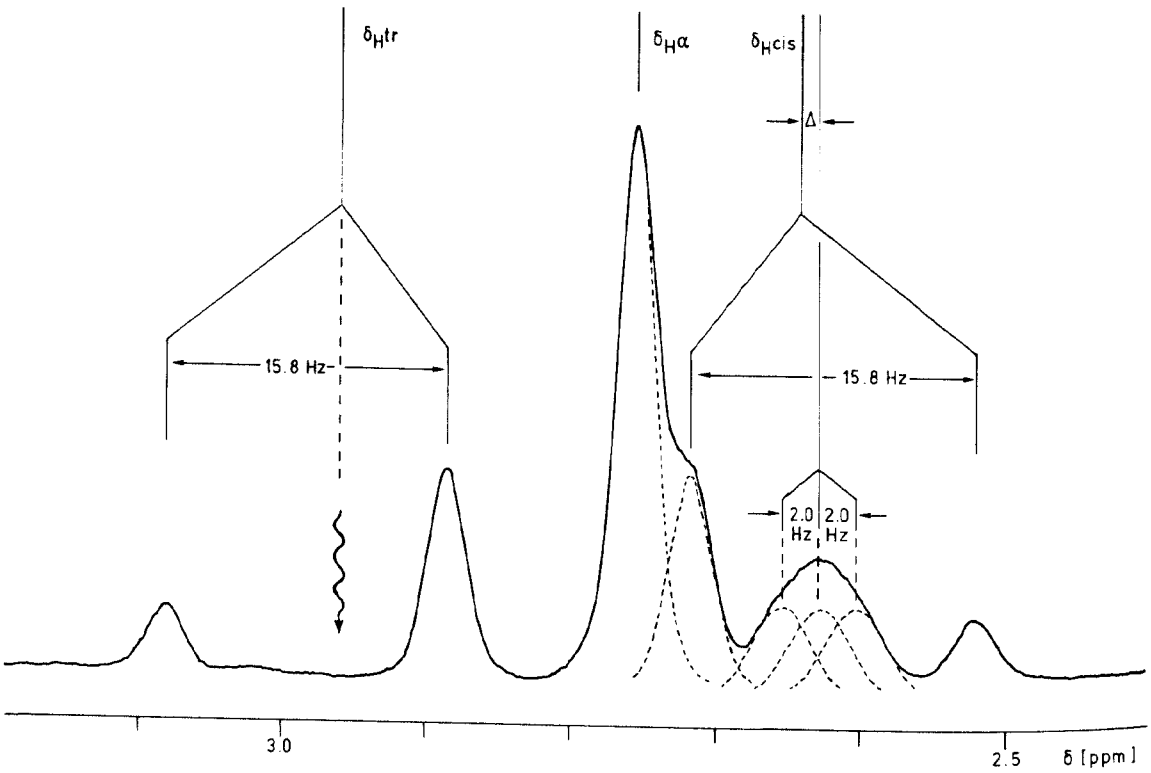
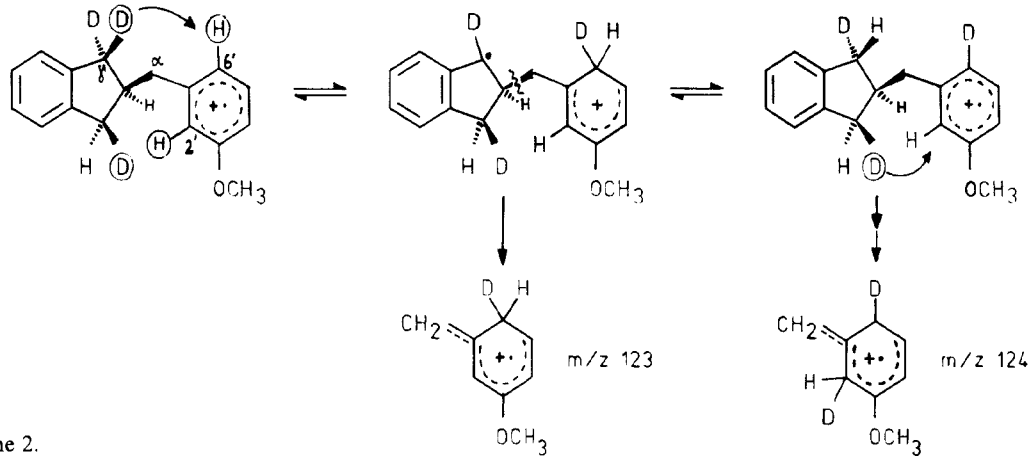


Fig. 1. Partial ^1H NMR spectrum (80 MHz) of **2a** (X = H).



Scheme 2.

3′-OCH_3) (Fig. 1 and Scheme 2). The 3′-methoxy derivative is discussed instead of the unsubstituted **2b** (X = H) for the sake of clearness [12].

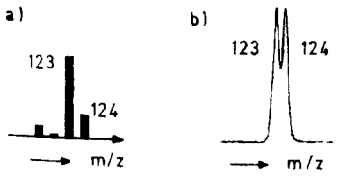


Fig. 2. Partial mass spectrum (70 eV) (a) and MIKE* spectrum (b) of **2b** (X = 3′-OCH_3), showing incomplete (a) and complete (b) exchange of the four hydrogen atoms (○) at C^{1cis}, C^{3cis}, $C^{2'}$, and $C^{6'}$ prior to fragmentation (*cf.* Scheme 2).

The major mass spectral fragmentation of ionized **2b** (X = 3′-OCH_3) is the formation of $C_8H_{10}O^{+\cdot}$ (*m/z* 122). This McLafferty type fragmentation requires the cleavage of the C^2-C^α bond, being preceded by the transfer of a hydrogen atom at a γ-position (*viz.* C^1 or C^3) to an *ortho*-position (*viz.* $C^{2'}$ or $C^{6'}$) of the alkyl anisole moiety [3]. This H^γ transfer has been shown to be reversible, leading to an exchange of the hydrogen atoms at the γ and the ortho positions, the extent of which increases with increasing life-time of the molecular ions [2, 3]. Because of steric reasons the hydrogen atoms *trans* to the benzyl group (H^{1t} and H^{3t}) cannot be transferred to the *ortho*-positions, restricting the exchange to only the four H^{1c}, H^{3c}, $H^{2'}$, and $H^{6'}$ atoms.

Whereas the hydrogen exchange is incomplete in the $\mathbf{2b}^{+\cdot}$ (X = 3′-OCH_3) molecular ions fragmenting within *ca.* 1 μs in the ion source of the mass spectrometer (Fig. 2a), it has reached equipartition in the long-lived (*ca.* 10 μs) *metastable* $\mathbf{2b}^{+\cdot}$ ions [13], fragmenting in the second field-free region of the instrument. This follows from the MIKE* spectrum of $\mathbf{2b}^{+\cdot}$ (X = 3′-OCH_3) (Fig. 2b) showing $C_8H_9DO^{+\cdot}$ (*m/z* 123) and $C_8H_8D_2O^{+\cdot}$ (*m/z* 124) exclusively and with the *statistically expected abundance ratio of unity*. As a consequence, the *cis*-positions of **2b** (X = 3′-OCH_3) must have been labelled completely ($\geq$ 98% D_2).

In accordance to this result, the reciprocally deuterated 2-(3′-methoxybenzyl)-[1*t*,2-D_2]-indane **2a** (X = 3′-OCH_3), bearing *no* deuterium atom at the *cis*-positions, shows $C_8H_{10}O^{+\cdot}$ (*m/z* 122) as the only fragment ions formed from the metastable molecular ions (Fig. 3).

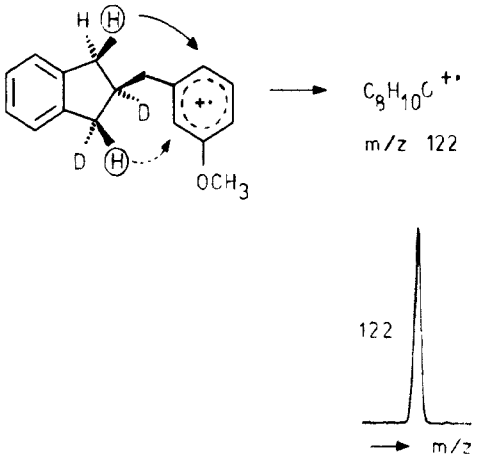


Fig. 3. Partial MIKE* spectrum of **2a** (X = 3′-OCH_3).

Conclusion

The results of the ^1H NMR and mass spectrometric analysis of deuterium labelled 2-benzyl-indanes (**2**) confirm independently that the homogeneous catalytic hydrogenation of 2-benzyl-indenes to 2-benzyl-indanes using $RhClP(C_6H_5)_3$ in benzene solution occurs with complete ($\geq$ 99%) regio- and stereospecifity. This warrants the use of this catalyst for deuterium (and tritium) labelling of all kinds of 1H-indenes in general.

Experimental

Melting points were measured with an Electrothermal melting points apparatus and are uncorrected. Boiling points were taken during the distillative purification using a Kugelrohr apparatus, Model GKR-50 (Büchi). All synthetic steps were recontrolled by thin layer chromatography (Kieselgel, Merck) mostly using petroleum ether/ethyl acetate (3/1) as eluent. IR-spectra were recorded with a Model 377 instrument (Perkin Elmer), ^1H NMR spectra with a WP 80 instrument (80 MHz, Bruker). 70 eV and low energy mass spectra were measured with a MAT 311 A instrument (Varian MAT) at 3 kV accelerating voltage, 300 μA emission current and *ca.* 250 °C ion source temperature. MIKE* spectra were obtained with a (high resolving) ZAB-2F mass spectrometer (Vacuum Generators) at 6 kV and 100 μA. Using this technique the magnetic sector selects the metastable ion which is to be investigated by its decompositions which occur after having passed the magnet. The ionic products thus formed are then analysed by scanning the following electrostatic sector field.

2-Benzyl-indene (**1**) was prepared according to Campbell *et al.* [14] by dehydration of 2-benzyl-1-indanol in 90% formic acid. This method cannot be applied to, *e.g.*, 2-(3'-methoxybenzyl)-1-indanol because of partial cyclodehydration to 4b,9,9a,10-tetrahydro-indeno[1,2-a]indene [15] which, however, can be omitted by heating the alcohol in dimethylsulfoxide (DMSO) [16]. The complete synthesis of the various substituted 2-benzyl-indenes and -indanes will be given in another context [15], restricting the present description to the preparation of the indanes discussed above.

2-(3'-Methoxybenzyl)-indene **1** (X = 3'-OCH_3)

2-(3'-Methoxybenzyl)-1-indanone was prepared as described by Thompson [17] as an oil (b.p. 160 °C/0.07 mbar [17]), which solidified within one day to give white crystals which had a m.p. of 58–59 °C after recrystallisation from ethanol.

2-(3'-Methoxybenzyl)-1-indanol was obtained by reduction of the ketone with $LiAlH_4$ in diethyl ether in 86% yield as an approx. 1:1 mixture of the *cis* and the *trans* isomers (white needles of m.p. 44–47 °C).

Calcd C 80.28 H 7.13,
Found C 80.37 H 6.99.

IR (KBr): ν (cm^{-1}) 3390 (br), 3020 (m), 2940 (s), 2840 (m), 1600 (s), 1580 (s), 1260 (s), 1150 (s), 1050 (s), 780 (m), 750 (s), 700 (m). The stereoisomers can be separated [15] but are easily identified in the mixture by ^1H NMR spectrometry ($CDCl_3$/TMS/D_2O) due to the resonance of their carbinol protons H^1): δ (ppm) 2.3–3.3 (mult., 5 H), 3.80 (sing., 3 H^{OCH_3}), 4.88 (dubl., $J_{H^1H^2}{}^{trans}$ = 6.0 Hz), 5.04 (dubl., $J_{H^1H^2}{}^{cis}$ = 4.8 Hz; 1 H^1), 6.6–6.9 and 7.1–7.3 (mult., 8 $H^{arom.}$). Mass spectrum (70 eV) of the mixture: *m/z* 254 ($M^{+\cdot}$; 5% B), 236 ($M^{+\cdot}-H_2O$, 4%) 133 ($M^{+\cdot}-CH_2C_6H_4OCH_3$, 30%), 122 ($C_7H_7OCH_3^{+\cdot}$, 100%), 121 ($C_7H_6OCH_3^+$, 32%). The mass spectrometric identification of the pure stereoisomers will be discussed in a separate paper [15].

The mixture of the stereoisomeric indanols (1.28 g, 5.0 mmol) was heated to 170–175 °C in 4 g (50 mmol) of dry, freshly distilled DMSO under N_2 atmosphere for 20 h. After cooling, the reaction mixture was worked up by adding water and extracting the emulsion with petroleum ether (50–70) several times. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent **1** (X = 3'-OCH_3) was obtained as an oil (b.p. 165–170 °C, 0.07 mbar), yield 0.93 g (78%). Recrystallisation from ethanol gave white crystals, m.p. 30–31 °C.

Calcd C 86.41 H 6.82,
Found C 86.71 H 6.66.

IR (neat): $\tilde{\nu}$ (cm^{-1}) 3055 (m), 2910 (m), 2840 (m), 1600 (s), 1585 (s), 1260 (s), 1155 (s), 1050 (s), 780 (m), 755 (s), 720 (s), 705 (m). ^1H NMR ($CDCl_3$/TMS): δ (ppm) 3.28 (br. sing., 2 H^1), 3.79 (quasi sing., 2 H^α and 3 H^{OCH_3}), 6.57 (br. sing., 1 H^3), 6.65–7.45 (mult., 8 $H^{arom.}$). MS (70 eV): *m/z* 236 ($M^{+\cdot}$, 42% B), 235 ($M^{+\cdot}-H$, 4%), 128 ($M^{+\cdot}-C_7H_8O$, 19%), 121 ($C_7H_6OCH_3^{+\cdot}$, 100%), 115 ($C_9H_7^+$, 12%), 91 ($C_7H_7^+$, 10%).

2-Benzyl-[1.1.3-D_3]-indene **1a** *(X = H) and 2-(3'-methoxybenzyl)-[1.1.3-D_3]-indene* **1a** *(X = 3'-OCH_3)*

5 mmol of the indene are added to a mixture of D_2O (99.75%, Merck) (3.0 g, 150 mmol), pyridine (5 g, distilled twice from CaH_2), and triethylamine (0.5 g, 5 mmol, freshly distilled, b.p. 87–88 °C). The tightly stoppered bulb was heated to 80 °C

(bath) overnight with stirring (some h will suffice to achieve equilibrium). The volatile components are removed carefully under oil pump vacuum. The residue, containing *ca.* 87% of the d_3-indene, is subjected twice to the same procedure and is then purified by recrystallization from ethanol (**1b** (X = H): yield 84%, m.p. 47–48 °C) or by short-path distillation (**1a** (X = 3'-OCH_3): 95%). Deuterium content is typically 99% (98.1% d_3, 1.8% d_2, by mass spectrometry, 9 eV electron impact ionization).

Homogeneous catalytic hydrogenation and deuteration of 2-benzylindenes **1** *and* **1a** *(X = H and 3'-OCH_3): 2-Benzyl-[1t,2-D_2]-indane* **2a** *(X = H)*

In a 10 ml cyclindric glass tube 210 mg (10 mmol) of **1** (X = H) are dissolved in 5 ml of dry benzene, and 45 mg (0.05 mmol) of $RhCl[P(C_6H_5)_3]_3$ are added. The tube is shut by a septum cap, connected to a microhydrogenation apparatus by a syringe needle adaptor and flushed with nitrogen and then deuterium gas. Under vigorous magnetic stirring the stochiometric amount of D_2 is absorbed at ambient temperature in *ca.* 12–15 h, but stirring is continued another 12–24 h until absorption has ceased. (Towards the end of the deuteration reaction the light-red solution gets deep-red, indicating irreversible reaction of the catalyst). The solution is filtered through kieselgel/benzene, the solvent then evaporated and the residue purified by Kugelrohr destillation (b.p. 145–150 °C/0.01 mbar), affording **2a** (X = H) as a colorless oil in nearly quantitative yield. ^{1}H NMR ($CDCl_3$/TMS): δ (ppm) 2.65 and 2.95 (AB-system, ^2J = −15.8 Hz, 2 H^3; see discussion), 2.64 (br. sing., 1 H^{1c}), 2.75 (sing., 2 H^a), 6.8–7.6 (mult., 9 $H^{arom.}$). Deuterium content (MS, 70 eV): 96.9% d_2, 2.2% d_1, 0.9% d_0 ≙ 98.0% [3].

2-(3'-Methoxybenzyl)-[1t,2-D_2]-indane **2a** *(X = 3'-OCH_3)*

This compound was obtained in the same way from the corresponding indene (**1**, X = 3'-OCH_3) as a colourless oil (b.p. 155–160 °C, 0.01 mbar). ^{1}H NMR ($CDCl_3$/TMS): δ (ppm) 2.65 and 2.97 (AB-system, ^2J = −16.0 Hz, 2 H^3), 2.63 (br. sing., 1 H^{1c}), 2.73 ppm (sing., 2 H^a and, in part, H^A), 3.76 (sing., 3 H^{OCH_3}), 6.7–6.95 (mult., 3 $H^{arom.}$) and 7.0–7.35 (mult., 5 $H^{arom.}$). Deuterium content (MS, 70 eV): 97.1% d_2, 2.7% d_1, 0.2% d_0 ≙ 98.5%.

2-Benzyl-[1c,3,3-D_3]-indane **2b** *(X = H) and 2-(3'-Methoxybenzyl)-[1c,3,3-D_3]-indane* **2b** *(X = 3'-OCH_3)*

These isotopomers were synthesized in the same manner by using the correspinding indenes **1a** (X = H and X = 3'-OCH_3) (see above) and H_2 gas. ^{1}H NMR ($CDCl_3$/TMS) of **2b** (X = H): δ (ppm) 2.6–2.85 (mult., H^2, 2 H^a), 6.9–7.45 (mult., 9 $H^{arom.}$); deuterium content (MS, 70 eV): 96.9% d_3, 2.7% d_2, 0.4% d_1 ≙ 98.8%. ^{1}H NMR of **2b** (X = 3'-OCH_3): δ (ppm) 2.6–3.0 (mult., H^2, 2 H^a), 3.78 (sing, 3 H^{OCH_3}), 6.7–6.9 (mult., 3 $H^{arom.}$) and 7.05–7.3 (mult., 5 $H^{arom.}$); D content (MS, 70 eV): 96.4% d_3, 3.0% d_2, 0.5% d_1, 0.1% d_0 ≙ 98.6%.

2-Benzyl-[1,1,2,3,3-D_5]-indane **2c** *(X = H)*

This isotopomer was obtained from **1a** (X = H) using D_2 gas. ^{1}H NMR ($CDCl_3$/TMS): δ (ppm) 2.75 (sing., 2 H^a), 6.8–7.6 (mult., 3 $H^{arom.}$). D content (MS, 70 eV): 87.1% d_5, 1.2% d_6, 11.1% d_4, 0.6% d_3 ≙ 97.8%.

The author thanks Professor Dr. H.-F. Grützmacher for support of this work. Discussions with him and with Professor Dr. H. Brockmann (Jr.) are gratefully acknowledged. Thanks are due also to Mr. G. Lipinski for measuring the ^{1}H NMR spectra and to Mr. H. Siffczyk for performing the elemental analysis.

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[7] As a marked example, the deuteration of 2-benzyl-[1,1,3-D_3]-indene **1a** (X = H, see scheme 1) in ethanol over palladium on charcoal (Merck) affords 19% [D_4]-, 68% [D_5]-, and 9% [D_6]-indane **2** (X = H); use of [D_6]-ethanol gives 7% [D_4]-, 83% [D_5]-, and 10% [D_6]-hydrocarbon.

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